REMARKS

Applicant respectfully requests entry of the amendments and remarks submitted herein. Claims 30, 39, and 48 are amended, and claims 1-29, 31-33, 35-36, 40-42, 44-45, 49-53 are canceled. Therefore, claims 30, 34, 37-39, 43, 46-48, 54-58 are currently pending.

Support for the amendment to claims 30, 39 and 48 reciting *Salmonella minnesota* can be found throughout the specification, such as, for example, in claim 33 and at page 7, line 15.

Rejection under 35 U.S.C. §112, Second Paragraph

The examiner rejected claims 30-38 under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the examiner indicated that the phrase "*Haemophilus influenzae*-specific lipooligosaccharide (LOS)" in claim 30 is indefinite. Claims 31-38 depend either directly or indirectly from claim 30. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Independent claim 30 as amended recites a process for the production of a lipooligosaccharide (LOS) which comprises the steps of: (a) growing in a culture medium *Salmonella minnesota* comprising (i) a core lipid structure containing a terminal heptose and (ii) a DNA sequence encoding an Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase (*rfe*), and (iii) an isolated DNA sequence encoding a lipooligosaccharide-synthesis gene G polypeptide (LsgG), wherein the DNA sequence encoding *rfe* is regulated by LsgG such that the LOS is synthesized by the addition of an acceptor molecule to the terminal heptose molecule; and (b) recovering the LOS from the culture medium.

The phrase "*Haemophilus influenzae*-specific" has been deleted from claim 30. Therefore, Applicant requests that this rejection be withdrawn.

Rejection under 35 U.S.C. §112, First Paragraph (Written Description)

The examiner rejected claims 30-50 and 52-58 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Claims 31-33, 35-36, 40-42, 44-45 and 52-53 have been cancelled. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Independent claim 30 is discussed above. Claims 31-33 and 35-36 have been cancelled. Claims 34, 37-38 and 56 depend either directly or indirectly from claim 30.

Independent claim 39 as amended recites a process for the production of a complex carbohydrate comprising the steps of growing in a culture medium *Salmonella minnesota* bacteria comprising (i) a core lipid structure containing a terminal heptose and (ii) a DNA sequence encoding an Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase (*rfe*), and (iii) an isolated DNA sequence encoding a lipooligosaccharide-synthesis gene G polypeptide (LsgG) from *Haemophilus influenzae*, wherein the DNA sequence encoding *rfe* is regulated by LsgG such that a complex carbohydrate is synthesized by the addition of an acceptor molecule to the heptose molecule; and recovering the complex carbohydrate from the culture medium. Claims 43, 46-47, and 57 depend either directly or indirectly from claim 39.

Independent claim 48 recites method comprising modifying a terminal heptose of a lipopolysaccharide (LPS) or lipooligosaccharide (LOS) core structure of a *Salmonella minnesota* bacterium gram-negative bacterial species, wherein the bacterium gram-negative bacterial species comprises a polynucleotide encoding an Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase (*rfe*) and an isolated DNA sequence encoding a lipooligosaccharide-synthesis gene G polypeptide (LsgG) from *Haemophilus influenzae*, wherein the polynucleotide encoding *rfe* is regulated by lipooligosaccharide-synthesis gene G polypeptide (LsgG) from *Haemophilus influenzae* such that an N-acetyl glucosamine is added onto the terminal heptose so as to modify the terminal heptose. Claims 54-55 and 58 depend either directly or indirectly from claim 48.

The Examiner cites to *University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1938 (Fed. Cir. 1997)* for the proposition that "a written description of an invention involving a chemical genus, like a description of a chemical species 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Applicant asserts, however, that when the claims recite a known gene, applicant need not recite the level of detail that would be required if one were claiming a previously-unknown gene.

The Federal Circuit held in *Capon v. Eshhar v. Dudas, 418 F.3d 1349, 1357 (Fed. Cir. 2005)* that in a written description analysis, one must take cognizance of the scientific facts, and

must consider the state of the scientific knowledge. In *Capon*, the court held that there was adequate written description because the claims recited a known gene. "The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. . . . Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." *Capon* at p. 1357. The "written description requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way." *Capon*, at 1358.

The present case is similar to *Capon*, and is distinguishable over *University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1938 (Fed. Cir. 1997)*, *Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993)*, and *Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (Fed. Cir. 1991)*. In *Lilly, 119 F.3d at 1567*, the cDNA for human insulin had never been characterized. Similarly in *Fiers, 984 F.2d at 1171*, much of the DNA sought to be claimed was of unknown structure, whereby the court viewed the breadth of the claims as embracing a "wish" or research "plan." In *Amgen, 927 F.2d at 1206*, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material.

The current claims, like those in *Capon*, recite a known gene. Therefore, Applicant asserts that since *rfe* was already known, one of skill in the art would have recognized that Applicant was in possession of the claimed invention at the time the application was filed. Thus, Applicant's disclosure in the specification as filed with respect to the *rfe* sequence, when read in the context of what was known to the art worker, satisfies the written description requirement of 35 U.S.C. §112, first paragraph.

The claims also recite that the gram-negative bacteria used in the methods comprise an isolated DNA sequence encoding a lipooligosaccharide-synthesis gene G polypeptide (LsgG) from *Haemophilus influenzae*. At page 6, lines 6-8, the specification discloses that the *lsgG* sequence from *Haemophilus influenzae* was available in the TIGR database, *i.e.*, *lsgG* was a known gene. Therefore, Applicant asserts that since *lsgG* was already known, one of skill in the art would have recognized that Applicant was in possession of the claimed invention at the time

the application was filed. Thus, Applicant's disclosure in the specification as filed with respect to the *lsgG* sequence, when read in the context of what was known to the art worker, satisfies the written description requirement of 35 U.S.C. §112, first paragraph.

The examiner indicates that the specification does not provide adequate support for the transformation of any or all gram-negative bacteria. Applicant disagrees with this statement. In order to expedite prosecution, however, Applicant has amended the claims to recite *S. minnesota.* Support for the recitation of *Salmonella minnesota* can be found throughout the specification, such as, for example, in claim 33.

Applicant, therefore, requests that this rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 30-32, 34, 36-41, 43, 45-47, 49-50, and 56-55 under 35 U.S.C. §102(b), alleging that those claims are anticipated by McLaughlin et al. (*Journal of Endotoxin Research, 1*, 165-174 (1994); hereinafter McLaughlin). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

The claims as presently amended recite that the production cell is a *Salmonella minnesota* bacterium. The Office Action dated 11/20/06 at page 12 concedes that McLaughlin et al. do not teach or suggest a method of *Salmonella minnesota.* Therefore, Applicant respectfully requests that this rejection be withdrawn.

Claims Rejections under 35 U.S.C. §103(a)

Claims 33, 35, 42, 44, and 52-55 are rejected under 35 U.S.C. §103(a) as being unpatentable over McLaughlin et al. (*Journal of Endotoxin Research, 1*, 165-174 (1994); hereinafter McLaughlin) in view of Preston et al. (*Critical Reviews in Microbiology, 22*, 139-180 (1996); hereinafter Preston) and Swierzko et al. (*Infection and Immunity, 61*, 3216-3221 (1993); hereinafter Swierzko). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

A rejection of obviousness under 35 U.S.C. § 103 requires that the Examiner establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner

has the burden to establish three basic elements. First, the Examiner must establish that there is some suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention. Second, the Examiner must establish that there is a reasonable expectation of success. Finally, the Examiner must establish that the prior art documents teach or suggests all the claim limitations. M.P.E.P. § 2143. Applicant respectfully submits that the Examiner has not demonstrated that the claims are *prima facie* obvious in view of the cited documents, for example, because the Examiner has not established that the prior art documents teach or suggest all the claim limitations, and because the Examiner has not established the suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention.

Applicant's claims are directed to the enzymatic synthesis of complex carbohydrates in a *Salmonella* bacterium. This claimed process involves the use of Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase and an LsgG regulatory protein. Applicant discloses that Undecaprenyl-phosphate N-acetyl glucosaminyl phosphate transferase catalyzes the transfer of N-acetyl glucosamine onto the carrier lipid undecaprenol phosphate. Applicant further discloses that expression of *rfe* is controlled by LsgG. By exploiting this interaction between *rfe* and *lsgG*, Applicant discloses that complex carbohydrates can be synthesized onto a core lipid structure containing a terminal heptose.

None of the cited references teach all of the elements of the pending claims, as none of the cited references teach the transformation of *S. minnesota*. Swierzko discloses the serological characterization of antisera collected from rabbits immunized with heat-killed *Salmonella minnesota* R4 chemotype Rd_2P^- (see Abstract and page 3218). Contrary to the statement on page 12 of the Office Action dated November 20, 2006, there is no teaching in Swierzko regarding the use of this bacterium as a transformant. *Salmonella minnesota* R4 chemotype Rd_2P^- is a spontaneous mutant of *Salmonella minnesota* R4. Swierzko does not teach transforming it with an exogenous gene. Moreover, Swierzko does not teach or suggest a process for the production of a modified LOS by using an exogenous gene, let alone using an *lsgG* gene (as recited in claim 30). Furthermore, Swierzko do not teach or suggest producing and recovering a complex

carbohydrate using *rfe* and *lsg* (as recited in clam 39). Nor does Swierzko et al. teach or suggest modifying terminal heptose of an LPS or LOS core structure using *rfe* and *lsg*, as recited in claim 48. Also, contrary to the statement on page 12 of the Office Action dated November 20, 2006, Applicant can find no teaching in Swierzko that this bacterium is a useful host due to their rapid growth in the laboratory.

McLaughlin and Preston do not remedy the deficiencies of Swierzko, as neither of these references teach or suggest the transformation of *S. minnesota*.

McLaughlin discussed the sequence of the *lsg* locus from *H. influenzae*. They identified eight open reading frames (ORFs) and performed transposon mutagenesis to try to begin to determine what, if any, function the products deduced from the ORF sequences might have. The authors of the paper did not have success in identifying the function of the deduced protein sequences encoded by the ORFs. McLaughlin at page 172 states that

> "it is most probably various sugar transferases expressed from the Hib *lsg* locus that are responsible for these modifications of the existing *E. coli* LPS. . . . Thus, it is likely that the *lsg* locus should contain a series of genes coding for sugar transferases. The sequence analysis of the 7.4 kb fragment and database search for the proteins homologous with the 8 ORFs, however, failed to show significantly high homology to any known sugar transferase, and it was not possible to deduce the functions of the products of the ORFs based on the sequence homology." (emphasis added)

McLaughlin later states that "future studies will be directed at defining the functions of the proteins expressed by the ORFs within this locus" (page 174). Thus, McLaughlin expected one or more of the ORFs to encode a sugar transferase, but that they could not find any significantly high homology to any known sugar transferase. Thus, at the time of publication, they could not determine the functions of the putative products encoded by the ORFs.

Applicant respectfully asserts that it was not until the experiments were performed by the present inventors that it was discovered that the LsgG protein was encoded by on of the eight ORFs. A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination. *In re Newell*, 891 F.2d 899, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). In deciding that a novel combination would have been obvious, there must be supporting teaching in the

prior art. *Id.* As discussed above, McLaughlin could not determine the functions of the putative products encoded by the ORFs. Thus, Mc Laughlin could not teach which specific ORF encoded LsgG. This information would be needed before the ORF could be isolate and then used to produce a LOS (claim 30) or a complex carbohydrate (claim 39), or to modify a terminal heptose of a lipopolysaccharide (LPS) or lipooligosaccharide (LOS) core structure (claim 48).

Further, as conceded by the Examiner at page 12 of the Office Action dated November 20, 2006, McLaughlin does not teach a method of transforming *S. minnesota* with a polynucleotide encoding an rfe from *H. influenzae*.

Preston does not remedy the deficiencies of McLaughlin or Swierzko. The Examiner refers to Table 4 on page 154 of Preston. However, Table 4 simply lists the *lsg* locus of *H. influenzae* and lists the function/comment with the *lsg* locus of expression of 6E4 epitope and lists *H. influenzae rfe* as being a homolog of LOS/LPS biosynthetic genes of other organisms. There is no teaching in Preston to take one of the listed loci and transform a different species of bacterium with it. There certainly is no teaching in Preston to specifically transform *S. minnesota.* Moreover, there is no teaching in Swierzko, Preston or McLaughlin that suggests that it would have been desirable or advantageous, or even suitable, to have expressed the *H. influenzae* lipooligosaccharide synthesis genes in *Salmonella.* Absent some motivation for modifying the prior art, the mere fact that the prior art could have been modified in the claimed manner does not render the claimed subject matter obvious.

None of these reference teaches the transformation of *S. minnesota*, and therefore do not teach all the claimed elements. Further, there is no suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify Swierzko and/or McLaughlin and/or Preston, or to combine the teachings of Swierzko and/or McLaughlin and/or Preston, so as to arrive at the claimed invention. McLaughlin does not teach that other bacteria could be substituted for *E. coli.* If one were to read Swierzko in conjunction with McLaughlin, one might be motivated to test the antisera generated by Swierzko against the LPS generated by McLaughlin. There is no teaching or suggestion, however, to substitute the *Salmonella minnesota* for *E. coli.*

Therefore, the pending claims are not obvious over the combination of McLaughlin et al., Preston et al., and Swierzko et al. Withdrawal of the 35 U.S.C. §103(a) rejection is respectfully requested.

CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

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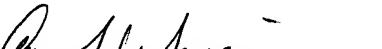
By: 
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